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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/628,225	07/28/2000	William W. Bachovchin	TUU-P01-006	3405

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EXAMINER	
RUSSEL, JEFFREY E	

ART UNIT	PAPER NUMBER
1654	

DATE MAILED: 09/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/628,225	BACHOVCHIN ET AL.	
	Examiner	Art Unit	
	Jeffrey E. Russel	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 April 2004 and 30 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *38-42 and 46-68* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *38-42 and 46-68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 July 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

ttachment(s)

) ☐ Notice of References Cited (PTO-892)

) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.

4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

5) ☐ Notice of Informal Patent Application (PTO-152)

6) ☐ Other: _____.

1. A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on April 22, 2004 and August 30, 2004 has been entered.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. Claim 42 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. There is no original disclosure of the cause of the glucose intolerance recited in instant claim 42. Applicants cite to page 51, line 6, of the specification as support for the amended claim limitation. However, the examiner has not been able to locate a copy of the cited article in order to determine whether or not it supports the claim limitation. (Applicants are requested to check the citation for this article, because the journal "Gastroenterology" lists Volumes 112 and 113, rather than Volume 35, as occurring in 1997.) Further, the citation in the specification is limited to mice, and there is no indication that a GLP-1 receptor gene deletion or disruption exists in glucose intolerant animals in general. Finally, it is not clear, from the brief summary of the article given in the specification, that the article supports both deletion and disruption of the gene encoding the receptor. In general, disclosure of a species (e.g., just mice,

or just gene deletion, or just gene disruption) does not constitute adequate written descriptive support for newly presented claims drawn to a genus encompassing the species.

4. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5. Claims 38-42 and 46-68 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 4-6, 8-14, 16-27, 30-36, 39, and 40 of copending Application No. 09/601,432. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '432 application anticipate the instant claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

6. Claims 38-42 and 46-68 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 39, 40, 43-64, 66-101, 103, 105-116, 119-121, 129-131, and 133-142 of copending Application No. 10/190,267. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '267 application anticipate the instant claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

7. Claims 38-42 and 46-68 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-90 of copending Application No. 10/794,316. Although the conflicting claims are not identical, they are not patentably distinct from each other. The '316 application claims administering the same protease inhibitors to the same patients, and claims that the protease inhibitors have an EC_{50} for modifying glucose metabolism which is at least one order of magnitude less than there EC_{50} for immunosuppression, but do not claim administering the protease inhibitors in amounts such that immunosuppression does not occur. It would have been obvious to one of ordinary skill in the art to administer the protease inhibitors in the claimed method of the '316 application in amounts such that glucose metabolism is modified but that immunosuppression does not occur, because it is routine in the pharmaceutical arts to minimize dosages of therapeutic agents so that side effects are minimized, and because the EC_{50} values claimed in the '316 application indicate that an immunosuppression side effect can be minimized by using a lower dose while still achieving the desired modification of glucose metabolism.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

8. The effective filing date of instant claims 38-41 and 46-68 is deemed to be February 2, 1998, the filing date of provisional application 60/073,409. Instant claims 38-41 and 46-68 are deemed to be entitled under 35 U.S.C. 119(e) to the benefit of the filing date of the parent

provisional application because the parent provisional application, under the test of 35 U.S.C. 112, first paragraph, discloses the claimed invention.

9. Claims 38-40, 46-53, and 68 are rejected under 35 U.S.C. 102(e) as being anticipated by Villhauer (U.S. Patent No. 6,011,155). Villhauer teaches treating non-insulin-dependent diabetes, i.e. Type II diabetes, and increasing glucose tolerance by administering a DPIV inhibitor having the same structure as Applicants' page 9, line 7 - page 11, line 10. The inhibitors improve early insulin response to oral glucose challenges. Oral administration of the inhibitors is taught. Daily amounts preferably range from 1-100 mg, and oral administration can be 1-3 times/day. Treatment begins with small doses which are then increased until side effects arise. See, e.g., the Abstract; column 9, lines 48-65; and column 10, lines 28-47. In view of the relatively small doses which are preferred by Villhauer, in view of Villhauer's teaching to begin with small doses of the DPIV inhibitor so that side effects are avoided, and in view of the lack of any reported immunosuppressive side effects in Villhauer, Villhauer is deemed inherently to administer DPIV inhibitors in amounts such that glucose metabolism is modified while not suppressing the immune system of the patient being treated. With respect to instant claims 38-40 and 47-50, in view of the similarity in structure and function between the DPIV inhibitor of Villhauer and Applicants' disclosed DPIV inhibitors, the EC50's and Ki for the DPIV inhibitors of Villhauer will inherently be the same as is recited in instant claims 38-40 and 47-50. Sufficient evidence of similarity is deemed to be present between the DPIV inhibitors and treatment methods of Villhauer and the inhibitors and methods recited in Applicants' claims to shift the burden to Applicants to provide evidence that their inhibitors and methods are unobviously different than the DPIV inhibitors of Villhauer. With respect to instant claim 40,

because the same active agents are being administered to the same animals according to the same method steps, inherently peptide hormone metabolism will be modified to the same extent in the method of Villhauer as is claimed by Applicants.

10. Claims 38-40, 46-53, and 68 are rejected under 35 U.S.C. 103(a) as being obvious over the German Patent 196 16 486. The German Patent '486 teaches using DP IV inhibitors to inhibit degradation of gastric inhibitory peptides and glucagon-like peptides, which effect can be used to reduce blood sugar levels and to treat diabetes mellitus. Inhibitors include alanyl pyrrolidide, isoleucyl thiazolidide, and N-valyl prolyl, O-benzoyl hydroxyl amine, and they can be administered orally. See, e.g., pages 1-2; page 10, line 21 - page 11, line 1; and page 11, line 15; of the attached translation. In view of the similarity in structure and function between the DPIV inhibitors of the German Patent '486 and Applicants' disclosed and claimed DP IV inhibitors, the EC_{50} and K_i values for the DP IV inhibitors of the German Patent '486 will inherently be the same as those recited in the instant claims. Sufficient evidence of similarity is deemed to be present between the DP IV inhibitors of the German Patent '486 and the inhibitors recited in Applicants' claims to shift the burden to Applicants to provide evidence that their inhibitors are unobviously different than those of the German Patent '486. The German Patent '486 does not teach administering its DPIV inhibitors in a single dose in amounts less than 2000 mg. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to determine all operable and optimal dosages and dosage schedules for the method of the German Patent '486 because dosage schedules are routinely determined and optimized in the pharmaceutical arts, and because it is desirable to minimize the number of administrations which are necessary for patient convenience and patient compliance. The

German Patent '486 does not teach administering its DPIV inhibitors in amounts such that glucose metabolism is modified but the immune system of the patient being treated is not suppressed. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to determine all operable and optimal doses for the treatment of the German Patent '486 because dose is an art-recognized result-effective variable which is routinely determined and optimized in the pharmaceutical arts. It would further have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to minimize the amount of DPIV inhibitor administered to the patients in the German Patent '486 because it is routine in the art to minimize doses so as to minimize side effects.

11. The obviousness rejection based upon the Balkan et al abstract (Diabetologia, Suppl. 40, A131 Abstract) in view of the WO Patent Application 93/08259 and further in view of Efendic et al (U.S. Patent No. 5,631,224) is withdrawn in view of the claim limitations reciting that the protease inhibitors are administered in an amount sufficient to modify glucose metabolism but not sufficient to suppress the immune system of the animal being treated. The WO Patent Application 93/08259 (see, e.g., page 21, lines 7-22) discloses the immunosuppressive properties of DPIV inhibitors, and does not suggest that there is a dosage or effective amount below which the inhibitors do not exhibit immunosuppressive properties yet still maintain their utility in treating Type II diabetes.

The obviousness rejection based upon the German Patent 196 16 486 is maintained. The declaration by Drucker under 37 CFR 1.131 filed April 22, 2004 and the declarations by Bachovchin and Plaut under 37 CFR 1.131 filed August 30, 2004 are not sufficient to antedate the German Patent '486 because the declarations do not allege that the acts relied upon to

establish the date prior to the reference were carried out in this country or a NAFTA country or a WTO member country. See MPEP 715.07(c). Also, it appears that the declarations are alleging that conception of the invention took place prior to the date of the Balkan et al abstract but that reduction to practice took place after the date of the Balkan et al abstract. This is uncertain because the Drucker declaration in section 3 indicates that conception took place prior to June 1997, but does not state how much prior to June 1997 the conception took place. Accordingly, it is not possible to determine whether the 6-month period of activity discussed in section 4 of the Drucker declaration concluded prior to or after the date of the German Patent '486. Assuming that the 6-month period concluded after the date of the German Patent '486, it is necessary for declarants to show evidence of facts establishing diligence between the time of conception and the time of actual reduction to practice. See MPEP 715.07(a). The declarations do not account, either with affirmative acts or acceptable excuses, for the entire period during which diligence is required. See MPEP 2138.06. The declarations do not contain evidence of diligence of the type discussed and found acceptable in this section of the MPEP.

The examiner maintains his position with respect to the remaining rejections for the reasons of record. See especially the final Office action mailed November 10, 1003 and the Advisory action mailed May 4, 2004.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey E. Russel at telephone number (571) 272-0969. The examiner can normally be reached on Monday-Thursday from 8:30 A.M. to 6:00 P.M. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Bruce Campell can be reached at (571) 272-0974. The fax number for formal communications to be entered into the record is (703) 872-9306; for informal communications such as proposed amendments, the fax number (571) 273-0969 can be used. The telephone number for the Technology Center 1600 receptionist is (571) 272-1600.

Jeffrey E. Russel

Primary Patent Examiner

Art Unit 1654

JRussel

September 16, 2004